PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 3 :
A61K 33/30, 35/78, 31/59
A61K 31/355, 31/315, 31/07

A1

(11) International Publication Number: **WO 84/ 02845**

(43) International Publication Date: 2 August 1984 (02.08.84)

(21) International Application Number: PCT/US84/00080

(22) International Filing Date: 18 January 1984 (18.01.84)

(31) Priority Application Number: 460,007

(32) Priority Date: 21 January 1983 (21.01.83)

(33) Priority Country: US

(71) Applicant: ADVANCED DRUG TECHNOLOGY CORPORATION [US/US]; 9333 North Meridan Street, Indianapolis, IN 46260 (US).

(72) Inventor: BILTON, Gerald, L.; P.O. Box 2345, Zionsville, IN 46077 (US).

(74) Agent: BIRDE, Patrick, J.; Kenyon & Kenyon, One Broadway, New York, NY 10004 (US).

(81) Designated States: AT (European patent), BE (European patent), CH (European patent), DE (European patent), FR (European patent), GB (European patent), JP, LU (European patent), NL (European patent), SE (European patent).

Published
With international search report.

(54) Title: VITAMIN-CONTAINING SKIN CARE OINTMENT

(57) Abstract

An oil-based ointment useful for wound-healing and to alleviate skin disorders which incorporates vitamins A, D, and E, a zinc salt, an aloe extract, and an organic astringent in admixture with a mixture of emollient oil carriers.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	**FR**	France	**ML**	Mali
AU	Australia	**GA**	Gabon	**MR**	Mauritania
BB	Barbados	**GB**	United Kingdom	**MW**	Malawi
BE	Belgium	**HU**	Hungary	**NL**	Netherlands
BG	Bulgaria	**IT**	Italy	**NO**	Norway
BJ	Benin	**JP**	Japan	**RO**	Romania
BR	Brazil	**KP**	Democratic People's Republic of Korea	**SD**	Sudan
CF	Central African Republic			**SE**	Sweden
CG	Congo	**KR**	Republic of Korea	**SN**	Senegal
CH	Switzerland	**LI**	Liechtenstein	**SU**	Soviet Union
CM	Cameroon	**LK**	Sri Lanka	**TD**	Chad
DE	Germany, Federal Republic of	**LU**	Luxembourg	**TG**	Togo
DK	Denmark	**MC**	Monaco	**US**	United States of America
FI	Finland	**MG**	Madagascar		

VITAMIN-CONTAINING SKIN CARE OINTMENT

Vitamins A and D and their derivatives have been used to alleviate the symptoms of skin rashes such as diaper rash and acne, and petroleum jelly-based ointments containing these vitamins are commercially available. However, an ointment which combines and optimizes the skin-conditioning and wound-healing properties of the oil-soluble vitamins has not heretofore been available.

It is therefore an object of the present invention to provide an emollient ointment for topical application which conditions, protects and moisturizes the skin, which alleviates proliferative and eruptive skin conditions, and which promotes wound healing.

Other objects, advantages and novel features of the present invention will be apparent to those skilled in the art from the following description and appended claims.

BRIEF DESCRIPTION OF THE INVENTION

The objects of the present invention are attained by the compositions of the present invention, which are oil-based ointments comprising a carrier mixture of both a penetrating and non-penetrating (barrier) emollient oil, and a polyhydric alcohol emollient; a mixture of

vitamins E, A, and D, a vitamin A-activating amount of a zinc salt, an aloe extract and an organic astringent. The emollients, vitamins, zinc salts, aloin and astringent function together to moisturize and protect normal skin, as well as to alleviate the symptoms of skin diseases and to promote the healing of wounds and burns when the ointment is applied topically.

DETAILED DESCRIPTION OF THE INVENTION

The ointments of the present invention comprise a mixture of three oil-soluble vitamins, vitamins E, A, and D, which are employed to promote the general healing of wounds such as cuts and scratches, and to reduce the severity of proliferative or eruptive skin diseases or disorders such as acne, psoriasis, impetigo, eczema, diaper rash, poison ivy, ulcers, sunburn or blisters and the like.

Together, the three pure vitamins or their corresponding, equivalently-acting analogs will comprise from about 5-20% of the ointments of the present invention, preferably from about 10-18%. Vitamin E will comprise the majority of the vitamin mixture, due to its efficacy as a wound-healer and its low toxicity, preferably comprising over 95% of the vitamin mixture, most preferably over 98% of the mixture. Vitamins A and D will preferably comprise less than about 2% of the vitamin mixture, most preferably less than 1%, e.g., about 0.03-0.15%.

The term "vitamin A" as used in the context of this invention is intended to include all of the biologically-active forms and analogs of this vitamin, including vitamin A_1 (retinol), vitamin A_2 (dehydroretinol), retinoic acid (tretinoin), 13-cis-retinoic acid, vitamin A acetate and vitamin A

palmitate.

Vitamin A is necessary for the normal growth of most cells of the body and especially for normal growth and proliferation of the different types of epithetial cells. When vitamin A is lacking, the epithelial structures of the body tend to become stratified and keratinized. Therefore, vitamin A deficiency manifests itself by scaliness of the skin and accompanying acne. Topical retinoic acid has been employed to effectively treat acne, due to its comedolytic action. Topical retinoic acid causes variable acanthosis, parakeratosis, disruption and thinning of the stratum corneum, erythema and increased skin permeability. Retinoic acid has been proposed for the treatment of variants of acne such as those induced by steroids, sunlight, and environmental pollutants such as tars and chlorinated hydrocarbons. See, J.W. Melski, et al., New England J. Med., 382, 503 (1980). Recently, 13-cis-retinoic acid has been demonstrated to be an effective treatment for cystic and conglobulate acne. Vitamin A will preferably be employed as vitamin A_1, vitamin A acetate, vitamin A palmitate or mixtures thereof in an amount from about 0.025-0.1% by weight of the ointment.

The term "vitamin E" as used in the context of the present invention is intended to include any of the biologically-active members of the vitamin E group, including d- or dl-alpha-tocopherol; d- or dl-alpha-tocopherol acetate or d- or dl-alpha tocopheryl acid succinate. Vitamin E is thought to aid wound healing by promoting tissue elasticity and continuity, thus reducing scarring. The use of topical vitamin E has also been proposed for the alleviation of pressure sores and ulcers (i.e., bedsores). Vitamin E is also believed to function as an antioxidant, thus stabilizing the vitamin A which is present. Vitamin E has been proposed

to be necessary for the effective absorption, transport and stroage of vitamin A. See, S.R. Ames, Amer. J. Clin. Nutr., 22, 934 (1969). Vitamin E will preferably comprise about 4-19% by weight of the present ointments, most preferably from about 9-17%.

The term "vitamin D" as used in the context of the present invention is intended to include the biologically-active vitamin D compounds or metabolites such as vitamin D_2, vitamin D_3, or 1,25-dihydroxycholecalciferol. Vitamin D mediates intestinal calcium absorption, bone calcium metabolism and muscle activity. Vitamin D has also been proposed as a facilitator of wound-healing via reducing scarring and increasing tissue elasticity. Vitamin D, preferably Vitamin D_3, will preferably comprise from about 0.001 to 0.1% by weight, most preferably from about 0.005 to 0.05% by weight of the ointments of the present invention. However, the vitamin D may be entirely eliminated from this formulation, if desired.

Other vitamins may also be added to this ointment, particularly vitamin C in the form of its palmitate. Vitamin C tends to promote healing and facilitate tissue oxygen transfer.

The ointments of the present inveniton are also formulated to comprise an organic or inorganic zinc salt. Useful zinc salts will include zinc acetate, zinc sulfate, zinc orotate, zinc oxide, zinc stearate, zinc carbonate, and mixtures thereof. Such salts function as skin cleansers and astringents, and have been employed topically to treat eczema, impetigo, psoriasis and varicose ulcers. Zinc salts have also been proposed to increase the level of retinol-binding protein, and thus to effect the activation and utilization of retinol. Thus, zinc salts and vitamin A have been used together

to treat acne. See, G. Michaelsson, et al., Arch. Derm., 113, 31 (1976); Brit. J. Derm., 96, 28.1 (1977). Zinc has also been proposed as an aid to the healing of surgical wounds. See, R.I. Henkin, New England J. Med., 291, 675 (1974).

Although an amount of zinc salt equal to about 1-10% by weight of the ointment is preferred, greater amounts of zinc salts may be employed, e.g., up to about 50% by weight of the ointment, where it is desired to enhance the cosmetic effects of the zinc salt and wherein the zinc salt or salts are selected to minimize local irritation due to the astringency of the salts. Alternatively, or in addition to the zinc salts, mercury, magnesium and selenium salts, primarily the oxides may be used, preferably in amounts from 0.01 to 10% by weight of the ointment.

The ointments of the present invention will also include about 0.01-10% by weight of an aloe extract, preferably from about 0.02-2.0% by weight of the extract, which is preferably incorporated as an aloe concentrate, e.g., aloe vera or aloe perryi concentrate. As defined herein, the term "aloe extract" refers to the inspissated juice of the aloe plant as well as to its dried concentrates which contain aloe-emodin, aloin or other active anthraquinone principles. Apart from their moisturizing properties, such extracts have been used to reduce thermal burn and sunburn inflammation and to enhance the healing of burns and wounds.

The ointments of the present invention will also comprise 0.05-5.0%, preferably 0.1-2.0% by weight of an organic astringent agent such as witch hazel extract, gallstannic acid, tannin, digallic acid, and the like. These compounds act to inhibit the pathological transcapillary movement of plasma protein, thus reducing

inflammation, edema and exudation.

The ointments of the present invention also comprise minor but effective amounts of antibacterial preservatives, such as about 0.025-1.5%, preferably 0.05-0.5% of a mixture of (C_1-C_4)-lower alkyl-4-hydroxybenzoates.

The above-described active ingredients are formulated so as to comprise about 5-40% by weight of the present ointments and are carried to and absorbed by the skin surface in admixture with about 60-95% of a carrier mixture of emollients.

Preferably, the emollient mixture will comprise a major portion, e.g. 35-75%, or 45-55% of a non-penetrating barrier-type emollient oil. Typical of such emollients are petrolatum, heavy mineral oils, paraffin wax, beeswax, and silicones, e.g., polysiloxanes. These oils rehydrate the skin by blocking the escape of skin moisture, lubricate the skin, and protect the skin from environmental irritants.

The emollient mixture will also include about 5-35% or preferably, 10-25% of a penetrating emollient oil, which effectuates the absorption of the active ingredients beyond the epidermal stratum. Such emollients include phytosterols, C_{20} - fatty acid coral (sea whip) extracts, and vegetable oils such as peanut, evening primrose, sunflower, sesame and safflower oils; and animal oils such as sperm oil and cod liver oil. A preferred class of penetrating emollient oils is the polyoxyethylene lanolin derivatives or the polyoxyethylene sorbitol/lanolin derivatives, which are described by G. Barnett in Cosmetics-Science and Technology, E. Sagarin, ed., Wiley-Interscience (1957) at pages 105-106 and 153, and in U.S. Pat. No. 2,478,820

the disclosures of which are incorporated by reference herein. Useful compounds of this type are formed by the condensation of about 10-80 moles of ethylene oxide per mole of lanolin or by the linking of sorbitol and lanolin with a polyoxyethylene chain containing 10-80 moles of ethylene oxide. For example, such compounds are commercially available from ICI Americas, Wilmington, Delaware as Atlas® G-1790 (20 moles of ethylene oxide/mole of lanolin), Atlas® G-1441 (40 moles of ethylene oxide linking sorbitol and lanolin) and Atlas® G-1471 (75 moles of ethylene oxide linking sorbitol and lanolin).

The emollient oil mixtures of the present invention will also include about 2-20%, preferably about 5-15% of a polyhydric alcohol emollient, e.g., a C_2-C_5 alkanol having 2-4 hydroxyl groups such as glycerol, sorbitol, propylene glycol and the like. These emollients soften the skin as well as aid in the solubilization and dispersion of the active ingredients in the carrier.

Therefore, preferred wound-healing emollient ointments will have about 5-35% of a mixture of active ingredients including 4-19% vitamin E, 0.025-0.1% vitamin A, 0.005-0.05% vitamin D_3, 1-10% of zinc oxide, 0.1-2% of powdered witch hazel extract, and 0.02-2% of aloe vera concentrate dispersed in about 65-95% of a carrier mixture comprising about 45-55% petrolatum, 10-25% ethoxylated lanolin, 5-15% glycerin and 0.05-0.5% of antimicrobial preservatives.

The ointments are typically prepared by preparing a stirred melt of the emollient oils and the polyhydric alcohol emollient, stirring in a homogeneous mixture of the zinc salt, the organic astringent, the aloe vera concentrate and the preservative, and then adding a mixture of the vitamins. When the stirred ointment

begins to solidify it is transferred to an ointment filler and tubed, i.e., into metallized plastic tubes.

The invention will be further described by reference to the following detailed example.

VITAMIN OINTMENT

A melt of 8615g of petrolatum, 3089g of ethoxylated lanolin and 2040g of glycerin was prepared in a stainless steel tub. To the stirred mixture was added a homogeneous mixture of 900g zinc oxide, 60g of powdered witch hazel extract, 60g of aloe vera concentrate, 18g of methyl-4-hydroxybenzoate and 18g of propyl-4-hydroxybenzoate. A mixture of 2465g vitamin E (1,100 I.U./g), 13.3g vitamin A (1.5×10^6 I.U./g) and 2.0g vitamin D_3 (1×10^6 I.U./g) was prepared and stirred for 5 minutes. The vitamin mixture was added with stirring to the remainder of the ingredients. The homogeneous mixture was stirred until solidification began, then transferred to a Colton ointment filler and filled into one-ounce tubes under 30 lbs. pressure.

The ointment of this invention has been used in the treatment of acne and of superficial wounds and bruises and has been reported as effective in providing symptomatic relief in such applications. The recommended mode of application is to cover the affected area with a thin layer of the ointment and optionally, to cover the wound with a sterile gauze. Alternatively, the ointment may be delivered by a depot technique, such as a skin patch containing a reservoir of the ointment for slow continuous release to and through the skin surface. In a further mode of application, the ointment is applied to the skin, which is then subjected to an ultrasound treatment by techniques well known in the art.

While certain representative embodiments of the invention have been described herein for purposes of illustration, it will be apparent to those skilled in the art that modifications therein may be made without departing from the spirit and scope of the invention.

I CLAIM:

1. An oil-based ointment comprising an active phase comprising:

   (a) a wound-healing amount of vitamin A;

   (b) an amount of vitamin E effective to stabilize and activate the absorption of said vitamin A;

   (c) an amount of an astringent zinc salt effective to increase the utilization of vitamin A;

   (d) an organic astringent;

   (e) an aloe extract; and

   (f) a carrier for said active phase comprising a mixture of a non-penetrating emollient oil, a penetrating emollient oil and a polyhydric alcohol emollient.

2. The ointment of claim 1 comprising vitamin D.

3. The ointment of claim 2 wherein the active phase comprises about 5-35% of said ointment and said carrier phase comprises about 65-95% of said ointment and wherein vitamin E comprises about 4-19% by weight of the ointment.

4. The ointment of claim 3 where the non-penetrating emollient oil comprises petrolatum, the penetrating emollient oil comprises a polyethoxylated lanolin derivative and the polyhydric alcohol emollient comprises glycerol.

5. The ointment of claim 2 wherein the zinc salt is selected from the group consisting of zinc oxide, zinc acetate, zinc sulfate, zinc stearate, zinc carbonate, zinc orotate and mixtures thereof.

6. The ointment of claim 2 wherein the organic astringent is powdered witch hazel extract.

7. The ointment of claim 3 comprising:

(a) about 9-17% vitamin E;

(b) about 0.025-0.1% vitamin A;

(c) about 0.005-0.05% vitamin D_3;

(d) about 1-10% zinc oxide;

(e) about 0.1-2% powdered witch hazel;

(f) about 0.02-2% aloe vera concentrate;

(g) about 45-55% petrolatum;

(h) about 10-25% polyethoxylated lanolin; and

(i) about 5-15% glycerin.

8. The ointment of claim 7 further comprising about 0.025-1.5% of an antibacterial preservative.

9. A method for alleviating the symptoms of a proliferating or eruptive skin disease by topically administering an effective amount of the ointment of claim 1.

INTERNATIONAL SEARCH REPORT

International Application No PCT/US84/00080

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all) [3]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int. Cl.[3] A61K 33/30, 35/78, 31/59, 31/355, 31/315, 31/07
U.S. Cl. 424/145, 195, 236, 284, 289, 344

II. FIELDS SEARCHED

Minimum Documentation Searched [4]

Classification System	Classification Symbols
U.S.	424/145, 195, 236, 284, 289, 344

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [5]

Handbook of Nonprescription Drugs, 5th Ed., 1977
Lexis Computer Search for Active Ingredients

III. DOCUMENTS CONSIDERED TO BE RELEVANT [14]

Category *	Citation of Document, [16] with indication, where appropriate, of the relevant passages [17]	Relevant to Claim No. [18]
Y	US, A, 3,878,197, published 15 April 1975, Maret	1-9
Y	US, A, 4,214,000, published 22 July 1980, Papa	1-9
Y	US, A, 4,154,823, published 15 May 1979, Schutt	1-9
Y	US, A, 4,224,319, published 23 September 1980, Marcadet	1-9
Y	N, Handbook of Nonprescription Drugs, 5th Edition, published 1977 by American Pharmaceutical Association, Washington, D. C., U.S.A., pages 356-359.	1-9

* Special categories of cited documents: [15]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search [2]	Date of Mailing of this International Search Report [2]
29 March 1984	05 APR 1984
International Searching Authority [1]	**Signature of Authorized Officer [20]**
ISA/US	Leonard Schenkman

Form PCT/ISA/210 (second sheet) (October 1981)